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ERCC2 rs13181 polymorphism association with glioma susceptibility in a Chinese population

X. Gao[1,2], Y.J. Tang[2], G.F. Zhang[2], L. Yu[1] and S.T. Qi[1]

[1]Department of Neurosurgery, Nanfang Hospital,
Southern Medical University Guangzhou, China
[2]Department of Neurosurgery, Jiujiang First People's Hospital, Jiujiang, China

Corresponding author: S.T. Qi
E-mail: qst_sjwk@126.com

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ABSTRACT. We conducted a case-control study to investigate the role of *ERCC2 rs13181* polymorphism in glioma development. A total of 165 patients who were histopathologically diagnosed to have gliomas and 330 controls were collected at Jiujiang First People's Hospital between July 2012 and June 2014. The *ERCC2 rs13181* polymorphism was analyzed using a polymerase chain reaction -restriction fragment length polymorphism assay. By conditional regression analysis, we found that the GG genotype of the *ERCC2 rs13181* polymorphism is associated with susceptibility to gliomas when compared to the TT genotype (OR = 2.05, 95%CI = 1.11-3.79). In the recessive model, the GG genotype is associated with an increased risk of gliomas when compared with the TT+TG genotype (OR = 1.87, 95%CI = 1.03-3.37). In conclusion, the *ERCC2 rs13181* polymorphism is correlated with an increased risk of gliomas in codominant and recessive models, which suggests that this polymorphism could influence the etiology of gliomas.

Key words: *ERCC2 rs13181*; Polymorphism; Glioma

INTRODUCTION

Gliomas are central nervous system neoplasms derived from glial cells. Gliomas are the most common type of brain tumor worldwide, accounting for about 80% of all malignant brain tumors (Bondy et al., 2008). Nearly 80% of glioma patients die within the first year after initial diagnosis (Pei et al., 2013). So far, the mechanisms underlying glioma tumorigenesis remain unclear. Exposure to ionizing radiation (IR) is considered arisk factor of gliomas (Liu et al., 2010). However, most patients with gliomas are not exposed to high doses of IR (Sadetzki et al., 2005), which suggests that genetic factors play an important role in glioma development.

Genetic factors, such as single nucleotide polymorphisms (SNPs), play an important role in modifying glioma susceptibility, such as SNPS in XRCC1, *ERCC1*, interleukin-8, and *VEGF* genes (Jiang et al., 2013; Yuan et al., 2014; Liu et al., 2015; Wang et al., 2015). The rs13181 polymorphism of *ERCC2* is a T to G substitution at the 751 locus, which may alter the enzymatic activity of the encoded protein. *ERCC2 rs13181* is associated with various cancers, such as gastric cancer, esophageal cancer, non-small cell lung cancer, hepatocellular carcinoma, prostate cancer, skin cancer, and bladder cancer (Yin et al., 2013; Zhu et al., 2013;Li et al., 2014; Ramaniuk et al., 2014; Zhu et al., 2014; Yang et al., 2015; Guo et al., 2015). Previous studies have reported the association between the *ERCC2 rs13181* polymorphism and glioma development, but the results are inconclusive (Caggana et al., 2001; Wrensch et al., 2005; Yang et al., 2005; Liu et al., 2009; Luo et al., 2013; Rodriguez-Hernandez et al., 2014). In our study, we conducted a case-control study to investigate the role of *ERCC2 rs13181* polymorphism in glioma development.

MATERIAL AND METHODS

Patients

We performed a case-control study. A total of 165 patients who were histopathologically diagnosed to have gliomas were collected at Jiujiang First People's Hospital between July 2012 and June 2014. The tumors were graded according to the World Health Organization (WHO) classification.

A group of 330 control subjects was randomly selected from the trauma outpatients and the annual check-up visitors in our hospital during July 2012 and June 2014. All of the control subjects were free of gliomas. Two control subject was matched by sex and age with a patient diagnosed with a glioma. The control subjects with a self-reported history of cancer or central nervous system-related diseases or those who previously underwent radiotherapy and chemotherapy for certain diseases were excluded from this study.

At recruitment, all participants were interviewed by trained nurses to collect detailed demographic information, such as smoking, drinking, and family history of cancer. The clinical characteristics of patients with gliomas were collected from medical records, such as histology types and tumor grade.

DNA extraction and genotyping

DNA was extracted from peripheral blood by salt extraction. The *ERCC2 rs13181* polymorphism was analyzed using a polymerase chain reaction (PCR)-restriction fragment

length polymorphism (RFLP) assay and the primers are as follows: 5'-TTG TGC TTT CTC TGT GTC CA-3' and 5'-CTA TCA TCT CCT GGC CCC C-3'. The PCR was performed in a 25-μL volume, including 3-4 μL genomic DNA, 0.1 μL Taq enzyme, 2.5 μL 10X Buffer, 2.0μ 25 M dNTP Mixture, 1.0 μL 0.5 μM forward primer and 1.0 μL 0.5 μM reverse primer. The amplification conditions were as follows: 94°C for 5 min, followed by 30 cycles of 94°C for 1 min, 55°C for 1 min, and 72°C for 2 min, followed by 72°C for 5 min. Enzyme digestion followed the identification process. The PCR products were digested with the *Msp*I restriction endonuclease and analyzed by electrophoresis in a 2% agarose gel stained with ethidium bromide and visualized under UV light.

Statistical analysis

The demographic and clinical characteristics of glioma patients and control subjects were compared by the chi-square and *t*-tests. The goodness-of-fit chi-square-test was used to analyze deviations from the Hardy-Weinberg equilibrium (HWE) of genotype distributions of *ERCC2 rs13181*. Conditional regression analysis was used to analyze the association between the *ERCC2 rs13181* polymorphism and glioma development. The results are reporteded by the odds ratio (OR) and 95% confidence interval (95%CI). The major homozygous genotype of the*ERCC2 rs13181* polymorphism was used as a reference. The interaction between *ERCC2 rs13181* polymorphism and environmental factors in the risk of gliomas was investigated using conditional regression analysis. Statistical analysis was conducted using the SPSS 21.0 package (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

The demographic and clinical characteristics of patients with gliomas and control subjects are shown in Table 1. By chi-square test we did not find significant differences between patients with gliomas and control subjects in terms of gender ($\chi^2 = 0.00$, $P = 1.00$), smoking status ($\chi^2 = 1.73$, $P = 0.19$), drinking status ($\chi^2 = 1.96$, $P = 0.16$), or family history of cancer ($\chi^2 = 0.80$, $P = 0.37$). There was significant difference between the two investigated groups in respect to age ($t = 2.34$, $P = 0.02$).

The association between *ERCC2 rs13181* and risk of gliomas is shown in Table 2. The genotype distributions of the *ERCC2 rs13181* polymorphism are consistent with the HWE in control groups ($P = 0.103$) (Table 2). In the codominant model, the genotype distribution ofthe *ERCC2 rs13181* was significantly different between glioma patients and control subjects ($\chi^2 = 6.07$, $P = 0.04$). In the recessive model, the distribution was also significantly different between the two groups ($\chi^2 = 4.82$, $P = 0.03$). By conditional regression analysis, we found that the GG genotype of the *ERCC2 rs13181* polymorphism is associated with susceptibility to gliomas when compared to the TT genotype (OR = 2.05, 95%CI = 1.11-3.79). In the recessive model, the GG genotype is associated with an increased risk of glioma when compared with the TT+TG genotype (OR = 1.87, 95%CI = 1.03-3.37).

By stratification analysis, we did not find significant association between *ERCC2 rs13181* polymorphisms and glioma development when stratified by age, gender, smoking, or drinking (All P values > 0.05) (Table 3).

Table 1. Characteristics of patients with glioma and control subjects.

Parameters	Cases	%	Controls	%	*t* test or χ^2-test	P value
Age, years	56.26 ± 13.48		53.37 ± 12.69		2.34	0.02
Gender						
Female	70	42.42	140	42.42		
Male	95	57.58	190	57.58	0.00	1.00
Smoking status						
Never	97	58.79	214	64.85		
Ever	68	41.21	116	35.15	1.73	0.19
Drinking status						
Never	109	66.06	236	71.52		
Ever	56	33.94	94	28.48	1.96	0.16
Family history of cancer						
No	143	86.67	295	89.39		
Yes	22	13.33	35	10.61	0.80	0.37
Histology type						
High grade	63	38.18				
Low grade	102	61.82				
WHO						
I-II	73	44.24				
III-IV	92	55.76				

Table 2. Association between *ERCC2 rs13181* polymorphism and development of glioma by logistic regression analysis.

Model	Patients	%	Controls	%	P for HWE	χ^2 value	P value	Crude OR (95%CI)[1]	P value	Adjusted OR (95%CI)[1]	P value
Codominant											
TT	80	48.48	189	57.27				1.0 (Ref.)	-	1.0 (Ref.)	-
TG	61	36.97	114	34.55				1.66 (0.88-3.12)	0.13	1.63 (0.86-3.09)	0.13
GG	24	14.55	27	8.18	0.103	6.07	0.04	2.10 (1.14-3.86)	0.02	2.05 (1.11-3.79)	0.02
Dominant											
TT	80	48.48	189	57.27				1.0 (Ref.)	-	1.0 (Ref.)	-
TG+GG	85	51.52	141	42.73		3.42	0.06	1.42 (0.98-2.07)	0.08	1.40 (0.96-2.05)	0.08
Recessive											
TT+TG	141	85.45	303	91.82				1.0 (Ref.)	-	1.0 (Ref.)	-
GG	24	14.55	27	8.18		4.82	0.03	1.91 (1.06-3.43)	0.04	1.87 (1.03-3.37)	0.04

[1]Ajusted for age and gender.

Table 3. Association between *ERCC2 rs13181* polymorphism and development of glioma stratified by demographic characteristics.

Variables	Patients		Controls		OR (95%CI)	P value	Spearman correlation coefficient	P value
	TT+TG	GG	TT+TG	GG				
Age								
<55	64	13	158	16	2.01 (0.91-4.41)	0.08	-0.042	0.35
≥55	77	11	145	11	1.88 (0.78-4.54)	0.16		
Gender								
Female	60	10	125	15	1.39 (0.59-3.27)	0.45	-0.045	0.32
Male	81	14	178	12	2.56 (1.14-5.79)	0.02		
Smoking status								
Never	80	17	198	16	2.63 (1.27-5.46)	0.01	-0.013	0.77
Ever	61	7	105	11	1.10 (0.40-2.97)	0.86		
Drinking status								
Never	93	16	220	16	2.37 (1.14-4.93)	0.02	0.051	0.26
Ever	48	8	83	11	1.26 (0.47-3.34)	0.65		

DISCUSSION

In the present study, we conducted a case-control study to investigate the association between ERCC2 rs13181 polymorphisms and the glioma development in a Chinese population. We found that the ERCC2 rs13181 polymorphism is associated with susceptibility to gliomas in codominant and recessive models.

The *ERCC2 rs13181* polymorphism may result in a defect in nucleotide excision repair. The role of insufficient DNA repair in carcinogenesis has been extensively studied (Xue et al., 2012). Xue et al. (2012) conducted a meta-analysis with 12 case-controls studies and found that the *ERCC2 rs13181* polymorphism is correlated with an increased risk of gastric cancer. Guo et al. (2015) conducted a meta-analysis with 21 case-control studies and reported that the*ERCC2 rs13181* polymorphism contributes to susceptibility to esophageal cancer. Li et al. (2014) performed a meta-analysis and reported that the ERCC2 rs13181 polymorphism is associated with susceptibility to lung cancer. Yang et al. (2015) conducted a meta-analysis with 11 case-control studies in an Asian population and reported that ERCC2 rs13181 could be a risk factor for hepatocellular carcinoma susceptibility. Zhu et al. (2014) performed a meta-analysis with ten studies and found that *ERCC2 rs13181* polymorphism is not associated with risk of skin cancer.

Several studies regarding the association between the *ERCC2 rs13181* polymorphism and gliomas have found inconclusive results (Caggana et al., 2001; Wrensch et al., 2005; Yang et al., 2005; Liu et al., 2009; Luo et al., 2013; Rodriguez-Hernandez et al., 2014). Caggana et al. (2001) conducted a case-control study in Americans investigating the association between *ERCC2* gene polymorphisms and risk of glioma and found that the*ERCC2 rs13181* polymorphism is associated with a risk of gliomas. Wrensch et al. (2005) conducted a study in Americans and reported that the*ERCC2 rs13181* polymorphism is correlated with the risk of glioma. Rodriguez-Hernandez et al. (2014) reported that the *ERCC2 rs13181* polymorphism may be a glioma susceptibility factor. The above studies have supported that *ERCC2 rs13181* polymorphism is associated with the development of gliomas. However, some studies report contrary results. Liu et al. (2009) conducted a study in an American population and reported that the *ERCC2 rs13181* polymorphism does not influence the development of adult gliomas. Luo et al. (2013) did not find a significant association between the *ERCC2 rs13181* polymorphism and risk of gliomas. The discrepancies of these results might be explained by differences in ethnicities, study design, and sample size. Further studies with participants from multiple locations and a larger sample size are needed to confirm our results.

In conclusion, we report that the *ERCC2 rs13181* polymorphism is correlated with an increased risk of gliomas in codominant and recessive models, which suggests that this polymorphism could influence the etiology of gliomas. However, studies with larger sample sizes are required to confirm these findings.

Conflicts of interest

The authors declare no conflict of interest.

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